IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Richter et al.

Application No. 10/573,365

Art Unit: 9460

Examiner: Young, Shawquia

Filed: March 5, 2007

For: NOVEL MACROCYCLES FOR THE TREATMENT OF CANCER

DECLARATION UNDER 37 C.F.R. § 1.132 OF WOLFGANG RICHTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

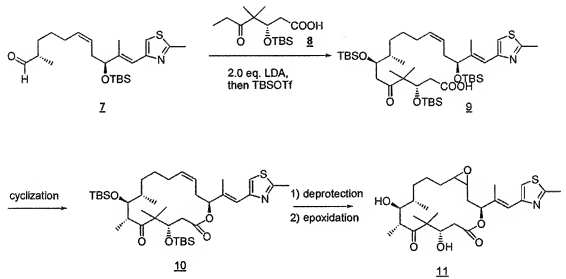
1. I, Wolfgang Richter, am the founder and Managing Director of R&D-Biopharmaceuticals GmbH, Martinsried, Germany, which is the assignee of the subject patent application, and I am one of the co-inventors of the subject matter disclosed and claimed in the subject patent application.

2. I hold a doctorate in Organic Chemistry from the Technical University Munich, and I have completed postdoctoral studies in Organic Chemistry at Stanford University.

3. The synthesis of epothilones and derivatives thereof has been well known in the art as evidenced by the recently published review article: Mulzer et al., *C.R. Chimie 11:* 1336-1368 (2008). The Mulzer reference discloses various synthesis schemes that have been disclosed in much earlier references that predate the earliest priority date available to the subject patent application, i.e., September 26, 2003. The compounds of the subject patent application can be prepared using these known synthesis schemes for epothilones by providing appropriate starting materials which can be prepared using methods that are well known in the art.

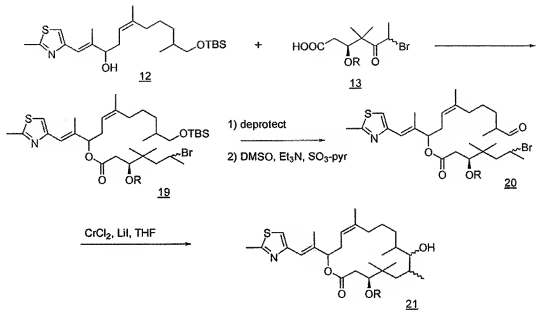
4. An example of a synthetic pathway to epothilones A and C was described in K.C. Nicolaou et al., Angew. Chem., Int. Ed. 35: 2399-2401 (1996). The Nicolaou reference discloses the following key reaction steps as set forth in Scheme 1:

Scheme 1



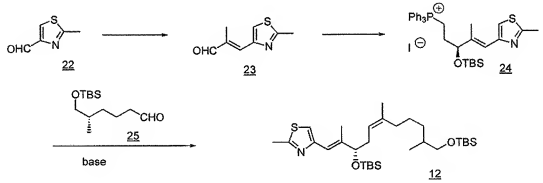
5. A second synthetic route to epothilones and analogs thereof appears in U.S. Patent Application Publication 2004/0082651 A1, which was published on April 29, 2004, based on International Patent Application No. PCT/EP01/11992, filed on October 16, 2001. The '651 publication discloses the following key reaction steps as set forth in Scheme 2:

Scheme 2



6. The preparation of fragment 12 from Scheme 2 is described in Scheme 3:

Scheme 3

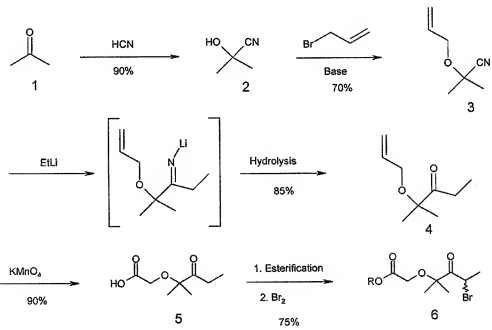


Fragment 7 from Scheme 1 is prepared from fragment 12 by (a) deprotection of the hydroxyl group and (b) Swern oxidation of the hydroxyl group to provide the corresponding aldehyde group.

The substitution of heteroalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaryl, or heteroarylalkyl aldehydes for 2-methylthiazole-4-carboxyaldehyde 22 will predictably lead to epothilone analogs having the recited moieties in place of the thiazole moiety found in naturally occurring epothilones.

7. For the synthesis of 3-O epothilone analogs, the preparation of the fragments 5 and 6 was conducted in our laboratories as described in Scheme 4:

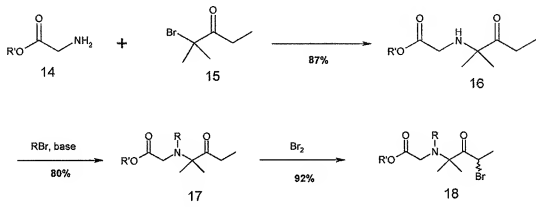
Scheme 4



The chemistry depicted in Scheme 4 was well known before the earliest priority available to the subject patent application, i.e., September 26, 2003. For example, addition of organometallic reagents (e.g., organolithium compounds) to nitriles to provide ketones (i.e., conversion of 3 to 4) is described in M.B. Smith and J. March, "Advanced Organic Chemistry," John Wiley & Sons, New York (2001), at page 1217. Oxidative cleavage of olefins to provide carboxylic acids (i.e., conversion of 4 to 5) similarly is described in the Smith and March textbook at pages 1525-1526. The halogenation of ketones (i.e., conversion of 5 to 6) is also described in the Smith and March textbook at pages 775-777.

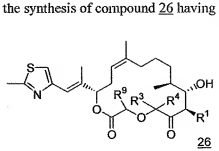
8. For the synthesis of 3-N epothilone analogs, the preparation of the fragments 17 and 18 was conducted in our laboratories as described in Scheme 5:

Scheme 5



The chemistry depicted in Scheme 5 was well known before the earliest priority available to the subject patent application, i.e., September 26, 2003. For example, the alkylation of primary amines to form secondary amines (i.e., reaction of 14 and 15 to form 16) and of secondary amines to form tertiary amines (i.e., reaction of 16 to form 17) is described in the Smith and March textbook at pages 499-501. The protection of the nitrogen atom of compound 16 to form 17, wherein R is acyl, silyl, and the like, is well known in the art. See, for example, T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, New York (1999), pp. 494-648.

9. The synthesis of the compounds recited in the subject patent application and the pending claims thereof can be readily accomplished by use of the synthesis methods identified herein. For example, the synthesis of compound 26 having the formula:



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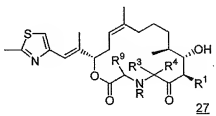
wherein R^1, R^3, and R^4 are methyl and R^9 is hydrogen, can be carried out using the chemistry depicted in Scheme 1 by substituting compound 5 from Scheme 4 for compound 8 in Scheme 1. Alternatively, the synthesis of compound 26 can be carried out using the chemistry depicted in Scheme 2 by substituting compound 6 from Scheme 4, wherein R is hydrogen, for compound 13 in Scheme 2.

10. Substituting C_2-C_4 alkyl groups for the methyl groups in compound 1 of Scheme 4, or replacing compound 1 of Scheme 4 with cyclopropanone or cyclobutanone, allows for preparation of compound 26 wherein R^3 and R^4 are independently hydrogen or C_2-C_4 alkyl, or, taken together, R^3 and R^4 form a cycloalkyl group with 3 or 4 ring atoms.

11. Substituting propyllithium, butyllithium, pentyllithium, cyclopropylmethyllithium, or cyclobutylmethyllithium for ethyllithium in Scheme 4 allows for preparation of compound 26 wherein R^1 is a C_1-C_4 alkyl group or a C_3-C_4 cycloalkyl group.

12. The synthesis of compound 27 having the formula:



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wherein R^1, R^3, and R^4 are methyl and R^9 is hydrogen, and wherein R is H, alkyl, or heteroalkyl, can be carried out using the chemistry depicted in Scheme 1 by substituting compound 17 from Scheme 5, wherein R' is hydrogen, for compound 8 in Scheme 1. Alternatively, the synthesis of compound 27 can be carried out using the chemistry depicted in Scheme 2 by substituting compound 18 from Scheme 5 for compound 13 in Scheme 2. The synthesis of compound 27 wherein R is OH can be carried out by preparing the compound of 28 wherein R is a protecting group, removing the protecting group, and oxidizing the amine to prepare compound 27 wherein R is OH, for example, by the methods disclosed in the Smith and March textbook at page 1539.

13. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: April 28th, 2009

Wolfgang Richter